The Urea a Feed Additive in the Ruminant Diet: Physiological Aspects of Metabolism

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Abstract

Feeding ruminants is the sector that absorbs the highest production costs, and the feed used as a source of nitrogen (protein-N) is the nutrient that requires the greatest investment. Furthermore, in tropical production systems, access to real protein is limited during the months of the year. The use of additives such as urea to supply non-protein nitrogen (NPN) in ruminant diets has been a strategy. However, despite containing 287.5 % protein, it requires specialized knowledge for its use in animal feed due to risks of toxicity. The regulation of ruminal pH and the availability of energy in the environment is related to the carbohydrates that reach the rumen via diet, this maintains the balance in the ruminal microbiota and guarantees the synthesis of microbial protein from NPN (urea). This chapter aims to provide basic knowledge to understand the digestion and metabolism of urea in the rumen, liver and associated factors involved in the process.

Keywords: Nitrogen, Catabolism, Anabolism, Ammonia, Toxicity

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Introduction

Urea as a Feed Additive

Ruminants are characterized by having a ruminal flora composed of microorganisms (bacteria, protozoa and fungi) that maintains a symbiotic relationship with the animal. This property makes it possible to use urea (formulae in Figure 1) as a feed additive for the supply of non-protein nitrogen (NPN). Urea contains 46% nitrogen, which represents 287.5% protein, an important element that rumen bacteria can biotransform into microbial protein and in this way only the ruminant has a rich source of protein in its diet (Nichols et al., 2022). Urea inclusion in the ruminant diet does not detract from the consumption of dry matter, because it does not modify and/or displease the taste of this additive to the animal. Tasting studies showed that cows did not reject the consumption due to the taste effect. Doses of 1350 mg of urea per cow daily did not affect voluntary feed consumption. The regulation of urea levels in the diet is rather carried out due to the risks of animal poisoning (between 1 and 3% of the total diet, it should not represent more than 20 or 30% of the nitrogen consumed daily), taking care not to exceed 25 mg/mL of ammonia at the ruminal level (EFSA, 2012; Shen et al., 2023).

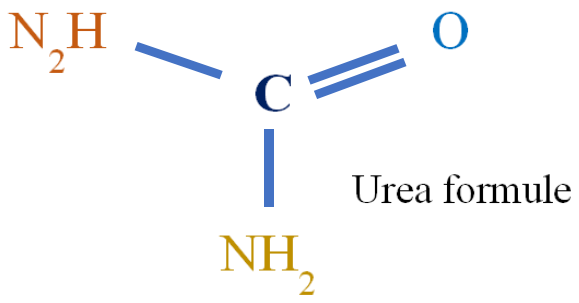

Fig. 1: Urea chemical formula (Adapted of EFSA, 2012)

Another way of supplying urea is in nutritional blocks following simple procedures to regulate consumption in animals without putting their health at risk, for example if we consider a consumption of 40 g/day for a 300 kg steer, then $40g\ x\ \frac{volume\ 100\%}{Required\ concentration\ 10\%} = 400\ g\ of\ block, with\ 10\%\ urea,$ this would be equivalent to 0.4 kg of block per animal per day, and would be projected to supply periods

or seasons and to batches of animals. The liquid form can also be used to provide this additive to the diet of ruminants, here proportions of molasses - urea are generally used in an average ratio of 8% on the molasses vehicle or excipient.

Saro et al. (2023) used normal and slow-release urea in sheep and observed that the molar proportion of propionic acid was higher and that of butyric acid was lower, and plasma urea was higher in lambs that received slow-release urea, although the parameter remained within normal ranges (10 to 35 mg/dL) for the species, without altering the acid-base balance in the blood (bicarbonate 21-28 mEq/L) (Jackson et al., 2002).

Urea in the Rumen, its Digestion and Metabolism

The availability of urea in the ruminal environment comes from different sources, the most important is through the diet by oral intake, another source is endogenous urea that is recycled from the liver by the bloodstream reaches the salivary glands and is recycled orally with saliva during the formation of the food bolus (figure 2 and 4), and another small proportion reaches the rumen directly through the portal system, this last process requires carrier proteins to be able to pass through the ruminal epithelium to the lumen (Patra & Haschenbach, 2018; Walpole et al., 2018), in this way, these proteins become a system that facilitates the transport of urea between the bloodstream and the rumen, to regulate the processes of recovery of urea nitrogen (Zhao et al., 2015). Urea in the ruminal environment begins to be digested by the action of the ureolitic microbial flora (approximately 50%) (Table 1) and the efficiency of utilization is determined by the capacity of the microflora to recycle NNP through hydrolysis (catabolic process by which urea is biotransformed to CO_2 and ammonia (NH_3)) and consequently the uptake of this compound for the synthesis of microbial protein usable by the ruminant (Figure 2 and Table 2) (Hailemariam et al., 2021; Pengpeng & Tan et al., 2013). The hydrolysis of urea to NH_3 and carbon dioxide (CO_2) is developed by the enzyme urease produced into the ruminal environment by species of ureolytic bacteria such as *Sphingobacterium, Herbaspirillum, Clostridium, Synechococcus* and *Paenibacillus* (Svane et al., 2020; Liu et al., 2020) and others shown in table 1. Ammonia is a toxic gas for animals and is characterized by having a pKa of 9.0. A study showed that the presence of this gas in the ruminal environment increased the pH from 6.5 to 7.4, that is, a positive relationship was maintained between the concentration of NH_3 and the pH (Shen et al., 2023; Abdoun et al., 2007), in addition, Plata (2024) demonstrated that the pH maintained a 97 % correlation and that the changes observed towards a slightly alkaline pH of between 7 and 8 were explained by 94% to the urea additive ($p<0.0001$), similar results were reported by Shen et al. (2023) who reported that ruminal ammonium concentration and pH are mutually dependent (Figure 2). Normally, what is sought is that the ammonia derived from the hydrolysis of urea is used by ruminal bacteria for the synthesis of amino acids and bacterial protein, however, for this to happen a series of interrelated factors must occur (energy supply in the diet, ruminal pH <6.5 and active ammonia-dependent microflora, mainly).

Table 1: Rumen bacteria with ureolytic activity

Ruminant specie	Ruminal bacteria
Cattle rumen	*Bifidobacterium (Lactobacillus) bifidum*[1]
	Bacteroides sp., Propionibacterium sp., Ruminococcus sp., Streptococcus bovis and Lactobacillus sp.[2], *Selenomonas ruminantium*[3], *Ruminococcus bromii, Bifidobacterium sp., Succinivibrio dextrinosolvens, Treponema sp., Butyrivibrio sp., Peptostreptococcus productus and Prevotella ruminicola*[4], *Clostridiaceae, Methylophilaceae Paenibacillaceae, Methylococcaceae, and Helicobacteraceae families Marinobacter and Methylophilus genera*[5],
Sheep rumen	*Staphylococcus sp., Streptococcus sp., Klebsiella aerogenes and Lactobacillus casei var. Casei* [6], *Staphylococcus saprophyticus and Micrococcus varians*[7].
Ruminant animals	*Ruminococcus albus*[8], *Selenomonas ruminantium* [9]

[1]Gibbons & Doetsch (1959); [2]Slyter et al. (1968); [3]John et al. (1974); [4]Wozny et al. (1977); [5]Jin et al. (2017), [6]Cook (1976); [7]Van Wyk & Steyn (1975); [8]Kim et al. (2014); [9]Smith et al. (1981); [10]Liu et al. (2020).

The pH and NH_3 Assimilation in the Rumen: It has been shown that a neutral pH (7.0 units) to slightly alkaline (8.0 units) increases the intraruminal concentration of ammonia, this increase favors the overpopulation of ureolytic bacteria over other groups of ruminal bacteria and facilitates the absorption of ammonia into the blood, which limits the use of urea as a source of NPN for the ruminant and, on the contrary, may favor the presentation of poisoning (Figure 2) (Shen et al., 2023; Nichols et al., 2022). When the intraruminal pH is maintained at 6.5, the ruminal flora remains in constant equilibrium and the portal absorption of ammonia is reduced by a decrease in the permeability of the ruminal epithelium (Shen et al., 2023). This regulation keeps ammonia absorption stable and within normal parameters without affecting the health of the animal and therefore the availability and use of ammonia in the ruminal environment for the synthesis of microbial protein by bacteria (Table 2) is more efficient (Shen et al., 2023). When there is no ingredient or additive in the diet that regulates the pH of the rumen, the absorption of ammonia (NH_4) through the wall into the bloodstream occurs by simple diffusion in a non-ionized liposoluble form (Figure 2) (Abdoun et al., 2007).

Microbial Protein Synthesis from NH_3: Ruminants as a complex organism do not have access to directly use the urea and ammonia nitrogen that reaches the rumen, but rather it is through the symbiotic relationship developed with the microorganisms found in this organ, that is, bacteria have the ability to capture free NH_3 in the ruminal deposit and use it to synthesize microbial proteins (Figure 2) (Saro et al., 2023). The urea biotransformed into ammonia is an important source of nitrogen, capable of regulating a minimum contribution of 8% required to maintain digestive activity and balance of the microbiota in the rumen (Dewhurst & Newbold, 2022). The incorporation of ammonia into the bacterial cell is a process in which NH_3 reacts to glutamate and glutamine and subsequently these compounds are incorporated into the biosynthesis of proteins (Figure 3) (Wu et al., 2024; Reitzer, 2003). This activity is intensively developed by a large group of ruminal bacteria

(Table 2). In order for bacteria to be able to use NH_3, the action of several enzymes is required, therefore, not all bacteria have the same capacity for utilization, some may be more active due to the type or types of enzymes they produce (relate Table 2).

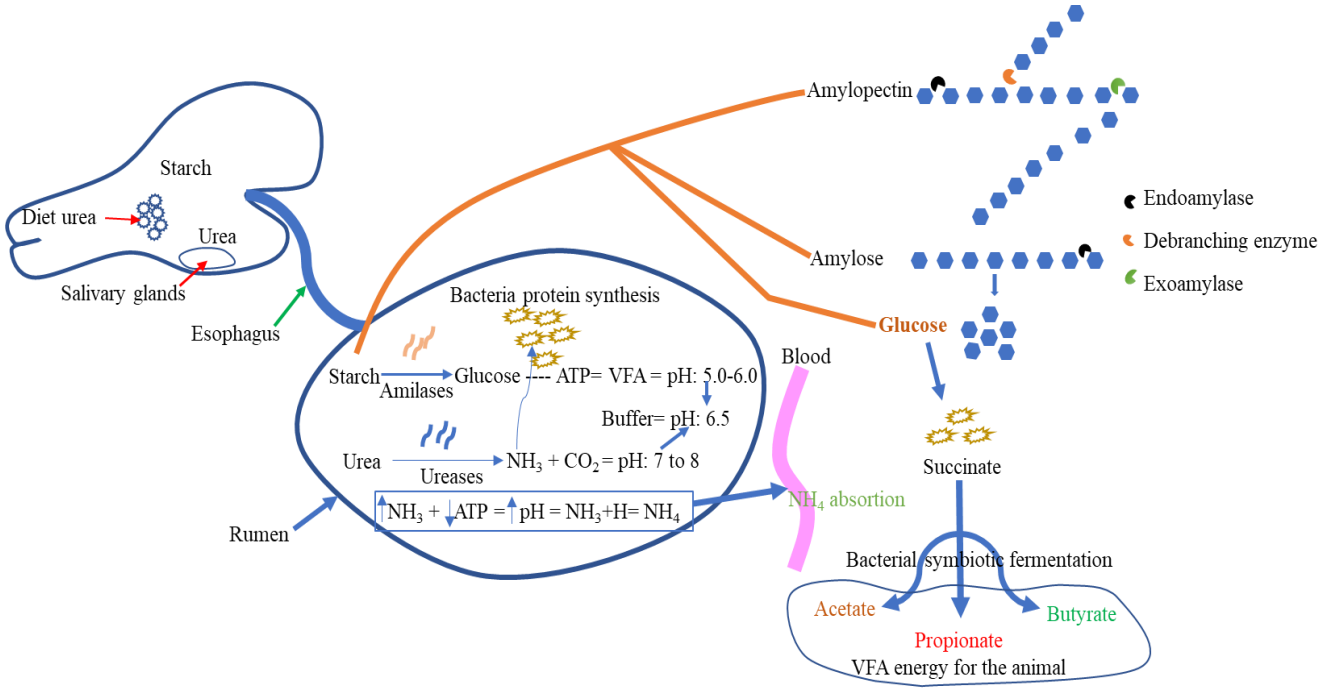

Fig. 2: Digestive and metabolic processes at the ruminal level related to the use of urea (Adapted of Pfau et al., 2023; Zhong et al., 2022; Hua et al., 2022; Patra & Aschenbach 2018)

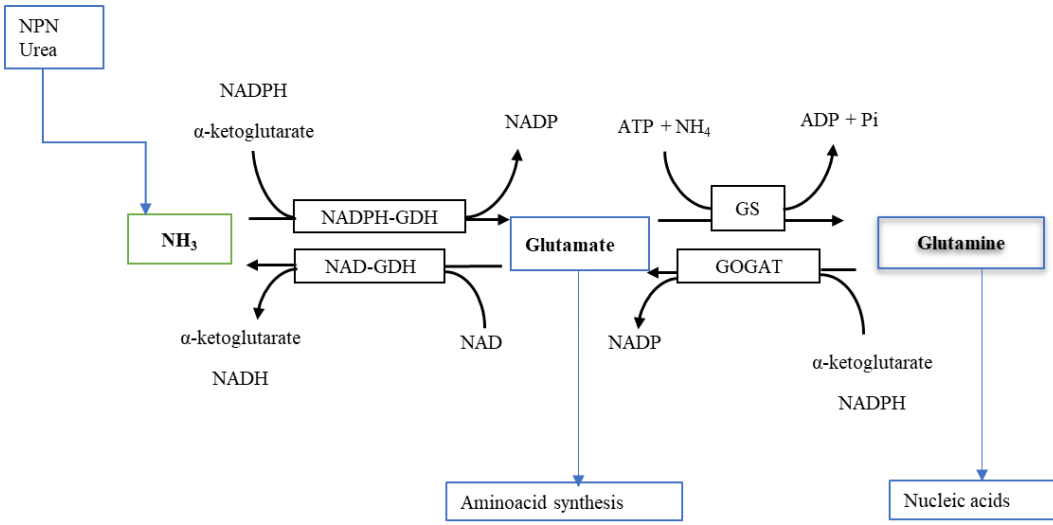

Fig. 3: Biotransformation of non-protein nitrogen (NPN) to ammonia and the assimilation process by ruminal bacteria (glutamate and glutamine) for bacterial protein synthesis in the rumen (Adapted of Wu et al., 2024).

For example, the enzymes glutamate dehydrogenase, glutamine synthetase and glutamate synthetase, which are very common in most bacteria, are related to NH_3 metabolism. Glutamate dehydrogenase catalyzes the incorporation of ammonia into α-ketoglutarate directly, while the transformation of glutamate into glutamine occurs through the action of the enzymes glutamine (GS) and glutamate synthetases (GOGAT) (Pengpeng & Tan 2014; Zhang et al., 2020). Although without much evidence, the action of other enzymes has also been linked to the process of ammonia assimilation by ruminal bacteria (Table 2), a core process, so that dietary urea can be made available to the ruminant as a microbial protein at the level of the small intestine (Dewhurst & Newbold, 2022). The reaction that catalyzes GS to amidate glutamate and synthesize glutamine requires a strong energy expenditure. When there is ammonium in the medium, the GS-GOGAT route is the most active for the assimilation of ammonia by ruminal bacteria (Figure 3). However, the availability of sufficient usable energy is essential (Purich, 2006). In a study developed by Reitzer (2003) determined that E. coli allocated approximately 15% of the cellular energy (ATP) available to the synthesis of glutamate and glutamine. Glutamate and glutamine are the main nitrogen-donating compounds for the synthesis of other amino acids (alanine, ornithine, citrulline, arginine, proline and aspartate, including the synthesis of purines and pyrimidines) and polyamines in cells (in

this case bacterial cell) important reactions for bacterial protein synthesis (Table 3) (Wu et al., 2024). It is believed that all the glutamate and glutamine recovered in the small intestine as a result of the drag of ruminal digesta (Microbiota) does not enter portal circulation, but is used in de novo synthesis to obtain a wide variety of amino acids (aa) (Table 3) (Wu et al., 2024).

Table 2: Main ruminal bacteria used ammonia and enzymes related to the process

Ruminal bacteria	Enzymes			
	Glutamate dehydrogenase	Glutamine synthetase	Glutamate synthetase	Other enzymes[1234]
Ruminococcus sp.	✓	✓	✓	1, 2, 3, 4
Ruminococcus champallensis	✓	✓	✓	2, 3
Methanobrevibacter ruminantium	✓	✓	✓	2, 3, 4
Fibrobacter succinogenes	✓	✓	✓	3, 4
Provotellla ruminicola	✓	✓	✓	1, 2, 3, 4
Selenomona ruminantium	✓	✓	-	1, 3
Streptococcus bovis	✓	✓	✓	2, 3, 4
Butyrivibrio fibrisolvens	✓	✓	✓	2, 3
Megasphera sp.	✓	✓	✓	-
Methanobrevibacter sp.	✓	✓	✓	2, 3, 4
Butyrivibrio sp	✓	✓	✓	2, 3
Micrococcus luteus	✓	✓	✓	1, 3
Treponema sp	-	✓	✓	2, 3, 4
Megasphaera sp	-	✓	✓	-
Mthanosphaera stadtmanae	-	✓	✓	-

[1]Enzymes Alanine dehydrogenase, [2]Asparagine synthetase, [3]Ammonium transporter, [4]Nitrogen regulatory protein PII. Reference: Adapted of Pengpeng & Tan et al. (2013), Hailemariam et al. (2021), Liu et al. (2020).

Table 3: Aminoacids (Aas) in feed and in ruminal bacterial proteins

Amino acids	Aas in feeds (g/100 g aa)		Aas in ruminal bacterial proteins(g/100 g aa)	
	Sheep	Cattle	sheep	Cattle
Alaine	6.53	8.02	6.74	6.72
Arginine	5.91	5.18	5.03	5.01
Asparagine	5.13	4.71	5.34	5.36
Aspartate	5.83	6.58	6.74	6.75
Cysteine	1.87	1.61	1.48	1.49
Glutamine	7.85	10.8	8.02	7.99
Histidine	2.18	2.28	2.05	2.07
Isoleucine	4.20	4.47	5.53	5.51
Leucine	8.32	8.67	7.67	7.66
Lysine	4.98	4.66	7.70	7.70
Methionine	1.63	1.79	2.42	2.40
Phenylalanine	4.90	5.30	5.13	5.16
Proline	7.93	4.9	3.67	3.66
Serine	5.05	4.56	4.65	4.62
Threonine	3.81	4.78	5.52	5.57
Tryptophane	1.24	1.53	1.39	1.38
Thyroxine	3.73	3.42	4.65	4.63
Valine	4.98	5.91	6.08	6.11

(Adapted of Wu et al., 2024)

***Energy substrate in the diet*:** energy as easily fermented carbohydrates in the ruminant diet is important for the assimilation and recycling of ammonia in the rumen; the normal concentration of this nitrogenous gas ranges from 0 to 130 mg/100 mL of ruminal content for adequate microbial crude protein synthesis (Zurak et al., 2023). In ruminants, a balanced diet in carbohydrates (starch) increases the flow of microbial protein to the duodenum (anabolism), at the expense of energy expenditure (catabolism of carbohydrates and sugars) (Firkins, 2021). On the other hand, the recycling of urea to the rumen via the blood, as mentioned above, requires the participation of transporter proteins such as aquaglyceroporins and UT-B transporters/channels present in the ruminal epithelium located in the cell membrane of the basal layer and this process is strongly activated when there is the presence of easily fermentable carbohydrates in the rumen (Figure 2 and Table 4) (Zhong et al., 2022).

In ruminants, the digestion of soluble carbohydrates (starch and sucrose) from the diet (corn, wheat, barley, molasses, among others)

takes place mainly in the rumen (Hua et al., 2022). In a study in cows, a ruminal starch digestibility between 57.7 and 94.5% was described, a variation that was attributed to the type of feed used as a source of carbohydrate (Moharrery et al., 2014). Huntington et al. (2006) described an apparent ruminal digestibility of starch between 75 and 80%, this background provides important information on the activity shown by the amylolytic flora on dietary carbohydrates to catalyze them to glucose (Figure 2).

Table 4: Relationship between carbohydrates in the ruminant diet and dietary urea metabolism

* Soluble carbohydrates	Effect on dietary urea metabolism
Low concentration of carbohydrates in the diet	Decrease: - Recycling of blood urea to the rumen - Microbial protein flow to the small intestine - Assimilation of NH_3 - Microbial protein synthesis Increase: - The pH of the rumen (7 to 8) - The NH_3 in the ruminal environment - The concentration of the ureolytic microflora - The diffusion of NH_3 into the blood - The risks of animal poisoning

(Fuente: Adapted of Mamua & Lee 2021; Hailemarian et al., 2021) *When soluble carbohydrate concentrations in the ruminant diet are adequate to high, the effects on dietary urea metabolism are reversed

Alternatively, diets supplemented with urea promote excess bacterial ammonia (NH_3) produced due to the degradation or hydrolysis of urea (ureases), which leads to an increase in rumen pH (Table 4). In this dietary scheme, glucose, fructose and other dietary carbohydrates (Table 5) are very important because the synthesis of bacterial protein from NH_3 requires a strong investment of energy (ATP) (Hailemariam et al., 2021). In addition, glucose and various carbohydrates captured by the bacterial cells of the ruminal flora, when catabolized by the bacteria, excrete Volatile Fatty Acids (VFA) into the ruminal medium (Table 5), which regulates the pH (maintained between 5.5 and 6.3), this modifies the metabolic effects on dietary urea expressed in Table 4 (Relate Figure 2). The VFA are available for the animal to be absorbed through the ruminal epithelium into the blood and used as energy fuels (Mamua & Lee 2021). Rathert-Williams et al. (2023) reported on a diet for finishing oxen with 2.8 Mcal in total and 13.5% crude protein, formulated with 45.8% corn grain, 36.7% cane molasses and 1.23% urea, basically maintaining the rumen pH between 6.26 and 6.37 and the production of VFA between 106.9 and 109.8 mM which corresponded mainly to 52 mol of acetate, 29 mol propionate and 15 mol of butyrate per 100 mol approximately. Mu et al. (2021) reported that increasing the use of energy concentrates from 40 to 60% in the diet of dairy cows reduced the pH from 6.13 to 5.7 and as a result of bacterial energy metabolism at the ruminal level, acetate decreased from 78.4 to 72.5 mM, propionate increased from 24.7 to 41.3 mM, butyrate showed a minor change from 13.2 to 14.6 mM. Mamua & Lee (2021) described that rumen bacteria use glucose, during metabolism it can be derived to succinate and with the intervention of the enzyme succinate dehydrogenase propionate and other alternate metabolites such as acetate and butyrate can be synthesized (Figure 4). The degradative activity on carbohydrates in the rumen is very intense, about 108 families of glycoside hydrolases have been identified (GH), 20 polysaccharide lyases and 11 glycosyltransferases; Of the 108 GH families, 19 were oligosaccharide-degrading enzymes, 18 were hemicellulases and debranching enzymes, 9 were cellulases and 7 were amylases (most abundant) (example starch ruminal digestion in Figure 2) (Mu et al., 2021).

Table 5: Fermentation characteristics of main ruminal amylolytic bacteria

Microorganism	Substrate	Fermentation product
Streptococcus Bovis	Starch, maltose, cellobiose, sucrose, glucose, fructose, galactose, mannose, lactose, (pectin, xylose, arabinose, mannitol, glycerol)	Lactate, CO_2 (acetate, formate)
Ruminobacter amylophilus	Starch, maltose	Formate, acetate, succinate (lactate)
Succinimonas amylolytica	Starch, maltose, fructose	Succinate (acetate propionate)
Selenomonas ruminantium	Maltose, cellobiose, Xylose, arabinose, glucose, fructose, galactose, mannose, lactose, mannitol, (starch, sucrose, glycerol, lactate)	Lactate, propionate, acetate, H_2 CO_2 (succinate)

(Adapted: Hua et al., 2022; Wang et al., 2021)

NH_3 metabolism in the liver: Dietary urea is rapidly degraded to ammonia and consequently absorbed through the rumen wall and causes toxic effects (Nichols et al., 2022). It has been proven that an increase in ammonia nitrogen at the rumen level increased the gram-positive Firmicutes and Actinobacteria, but reduced the gram-negative Fibrobacteres and Spirochaetes due to an increase in pH, a situation that favored the flow of NH_3 to the bloodstream as NH_4 (Shen et al., 2023). The ammonia absorption above normal limits in the blood cause hyperammonemia and it is the liver's job to remove this compound from the circulation and avoid a case of ammonia toxicity (Kopylchuk et al., 2020). The ammonia biotransformation in the liver occurs through the intervention of the enzymes carbamoyl phosphate synthetase and glutamine synthetase, where it is transformed into urea (non-toxic form) and subsequently eliminated in the urine in greater proportion; this is the most active elimination route when the concentration of ammonia in the rumen (50 mg/L) and blood (0.5 mM) is around the normal

limits of its concentration (Nichols et al., 2022). When the concentration of NH_3 in the rumen is low, then the urea recycling routes liver – blood – salivary glands and liver – blood – ruminal epithelium become priority (Pfau et al., 2023). Not exceeding the liver's capacity to metabolize free ammonia in the blood (toxic compound) reduces the risks for the animal (Ma & Faciola 2024). Ammonia detoxification at both the ruminal and systemic levels have implications for energy metabolism since in both cases there is energy expenditure (catalysis) in the anabolic processes that occur (urea synthesis), this expense must be rectified to avoid negative implications in the final production of the animal. Ammonia is reconverted through the urea cycle for excretion, mainly renal (Gimelli et al., 2023; Heidari et al., 2023). An irregular increase in the production and absorption of ammonia, generally within the first two hours after feeding, overloads the hepatocytes, leading to the accumulation of NH_4 in the blood (2.5 to 4.0 mg/100 mL) and triggering a rapidly developing intoxication problem (Shaikat et al., 2012). The urea cycle is the most important pathway for removing NH_4 from the circulation and several enzymes and two mitochondrial transporters are involved in this process. This process catalyzes the cyclic conversion of an ammonia molecule, aspartate and bicarbonate into urea, a stable compound that is easily excreted in urine (Figure 4 of the urea cycle) (Cholico et al., 2024; Rossignol et al., 2020)

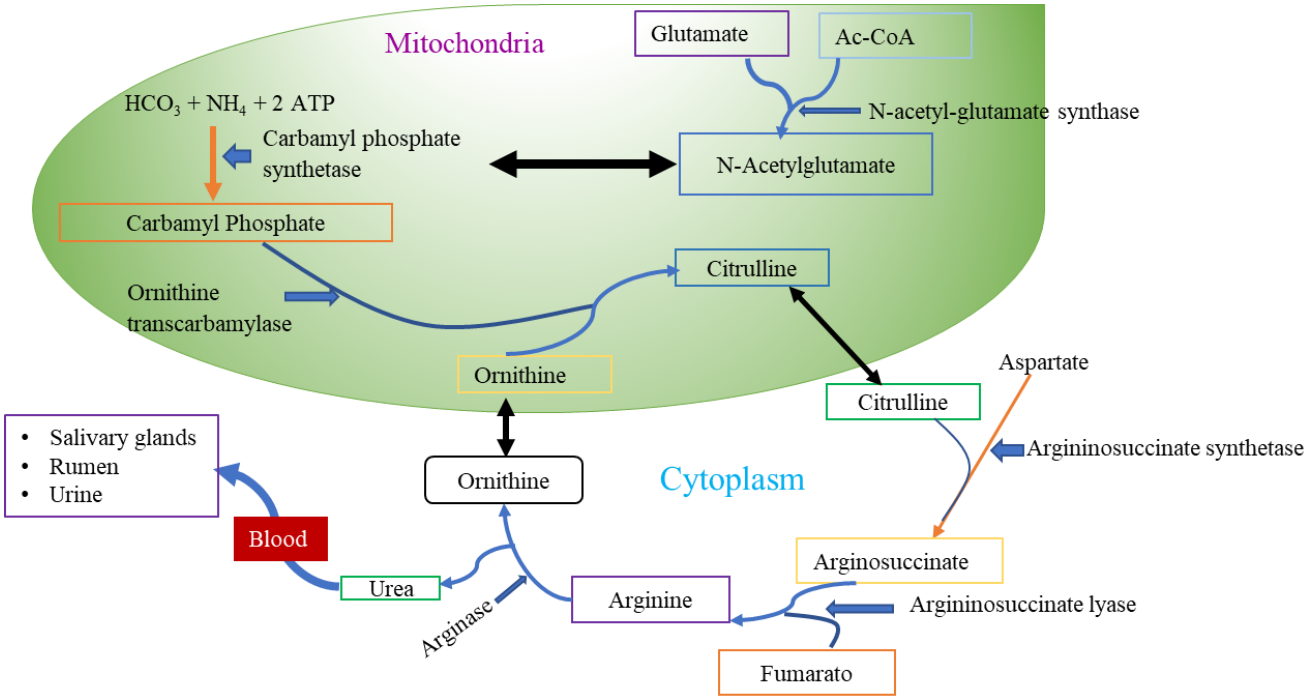

Fig. 4: Live urea cycle in ruminants, six enzymes action (Adapted: Cholico et al., 2924 & Rossignol et al., 2020)

NH_4 toxicity: Toxicity cases in ruminants occur due to an inadequate mixture of NPN (urea) in the diet, errors in dosage when preparing the diet, management of heterogeneous groups animals (hierarchy and competition for feed), no adaptation period and low-energy diets (Ma & Faciola 2024). Strategies have been developed to reduce the chances of poisoning when urea is used as an additive in feed diet. The formulation of slow-release urea compounds is intended to modify, condense, coat or encapsulate urea to delay hydrolysis in the rumen and thereby ration ammonia levels for microbial protein synthesis (Joysowal et al., 2019; Cherdthong & Wanapat, 2010). Xin et al. (2010) reported that *in vitro* concentrations of NH_3-N were lower when using polyurethane-coated urea, and *in vivo* in dairy cows the blood urea concentration (16.7 mg/dL) was lower than in cows fed feed grade urea. Huntington et al. (2006) demonstrated that using a urea-calcium complex regulated urea hydrolysis in Angus oxen and therefore did not change the pH in the rumen (6.5) and reduced plasma concentrations of NH_3-N by 1.6 times compared to animals that received free dietary urea. Kardaya et al. (2012) reported that a zeolite-bound urea compound reduced rumen NH_3 concentrations (11.5 mM) and pH (6.7) in lambs compared to animals on a urea-free diet. The background demonstrates that these technologies can prevent and/or reduce the risks of poisoning when urea is used as a feed additive in ruminants. The breakdown of urea into ammonia by urease is up to four times faster than its use by ruminal microorganisms (Gimelli et al., 2023).

Ammonia in high serum concentrations is neurotoxic (between 2.5 to 4.0 mg/100 mL) and triggers a rapid course of intoxication between 20 to 60 minutes in cattle and 30 to 90 min in sheep and a pH >7.5 generally (Thompson, 2017), which contributes to altered brain energy, morphological changes in astrocytes and the interruption of the glutamate-glutamine cycle for the synthesis of amino acids in protein anabolism (Kroupina et al., 2022); The central nervous system is the main target of NH_4 toxicity (Heidari et al., 2023). Rossignol et al. (2020) reported that NH_4 can cause cerebral edema and prolonged exposure neurological injury. In hyperammonemia, ammonia is able to cross plasma membranes through diffusion, channels and transport mechanisms and thus alter cell pH. The intracellular mechanisms that trigger the toxic effects have been linked to the mitochondria, where ammonia depolarizes the mitochondria and depletes the ATP supply to the cell and induces mitochondrial permeabilization, in the energy imbalance it inhibits the activity of the mitochondrial transport chain and the enzymes of the Kreb's cycle, leading to cell death (Heidari et al., 2023). There are reports that NH_4 also causes metabolic alkalosis and increases the affinity of hemoglobin for oxygen leading to tissue hypoxia. Kopylchuk et al. (2020) reported that ammonia via blood crosses the blood-brain barrier and

accumulates in the brain, triggering various side effects and encephalopathy. Zhang et al. (2022) discovered that the rate of cell apoptosis in blood lymphocytes increased by 124 to 481% in animals exposed to concentrations of 5 to 10 mM ammonia compared to controls. Li et al. (2021) reported that ammonia in pigs caused oxidative stress problems by decreasing the concentrations of the antioxidant glutathione, responsible for the reduction of free radicals, and its cofactor action also decreases the actions of enzymes such as glutathione peroxidase and superoxide dismutase. General symptoms are ruminal atony and tympany, muscle tremors, spasms and convulsions with abdominal pain, polyuria, bruxism, pulmonary edema leads to marked salivation, dyspnea, panting, cyanosis and death with a course of 2 hours in cattle and up to 4 hours in sheep, non-dominant animals with minor ingestion of the additive may recover 12 hours later (Thompson, 2017). In treatment, removing nitrogenous substrate from the diet, the use of acetate, citrate, aspartate or glutamate, keep the urea cycle active and help lower ammonia levels in a short time. Ponnuswamy et al. (2022) used a therapy affected cow showed a ruminal pH of 9.7, with 5 to 8 L of 5% acetic acid diluted in 20 Lt of cold water intraruminally inactivates ureases and reduces NH_4 absorption, plus IV Ringer's lactate 5 L/d^{-1}, Calcium (24 mg/mL) and magnesium (0.18 mg/mL) gluconate (volume 100 mL) IV slow, are also recommended (Mazagão et al., 2023).

Conclusions

Urea is an important additive that supplies nitrogen to the ruminant diet, however, to promote its balanced metabolism it is necessary to promote the rationed use by ruminal bacteria (adequate dosage and formulate urea-based complexes). By regulating consumption and in the form of a complex, hydrolysis is slower and more prolonged, which regulates the accumulation of ammonia in the rumen. In addition, the contemplation of the availability of easily fermented carbohydrates so that bacteria obtain energy for protein synthesis from NH_3 with the release of VFA to buffer the ruminal pH (<6.3), allows controlling the absorption of ammonia in the form of NH_4 into the bloodstream and reducing the risks of animal poisoning

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